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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/560,288	04/27/00	HANLEY E	8151-24A

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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	3

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/560,288	Hanley Jr. et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Apr 27, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-34* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-34 are presented for examination.

Priority

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicants are required to update the status of U.S. Patent Application Serial No. 08/979,674 to indicate that it is now U.S. Patent No. 6,080,579.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to therapeutic compositions of cultured human intervertebral disc cells for use in treating human intervertebral disc diseases and methods of treating human intervertebral disc diseases by implanting the cultured human intervertebral disc cells into a target disc area needing treatment.

The specification discloses methods of isolating human intervertebral disc tissue, isolating representative regions of annulus and nucleus, and culturing the regions as explants *in vitro* as monolayers (see, e.g., page 5, lines 8-21). Monolayers are further trypsinized, and seeded in alginate to form a three dimensional structure comprising alginate and cells (see, e.g., pages 6-8). The cells, either obtained from the monolayer culture system or the three-dimensional culture system, are loaded into an "implantation carrier" for insertion into the target disc area. The implantation carrier can be any material or structure suitable as a transplantation carrier to facilitate the implantation, adhesion, migration, and survival and growth of the implanted cells (see, e.g., pages 8-9). The specification also discloses that the three-dimensional structure used in propagating human disc cells can be used as a three-dimensional construct for implantation purposes. The specification indicates that "after the disc cells have proliferated and re-expressed extracellular matrix materials in the three-dimensional structure to a desired extent, the three-dimensional structure can be implanted directly to the desired area in the patient" (see, e.g., page 9, lines 17-23); that "the size and shape of the three-dimensional construct to be implanted should be adapted to the target area of implantation such that the pressure, volume, degree of disc distention, and the like in the area are appropriate after the implantation"; that "it is important to ensure that the implanted construct is such that the nerve root in the area is not compressed excessively"; and that "the cell density in the implantation carrier should be selected such that the cells will be capable of surviving, growing, and differentiating to from a healthy tissue filling the void created by the diseased tissue or the removal of a disc tissue without causing any significant undesirable compression against any nerve root or other tissue structures in or near the implantation area" (see, e.g., page 10, lines 18-30). The specification provides two example of implanting autologous disc cells contained in the implantation carrier GELFOAM in the disc site

of sand rats. In these experiments, the specification states that "Cells were grown through primary explant and P1 passages" (see page 17, lines 7-9). However, the specification does disclose if the cultured cells are annulus or nucleus cells, if the implanted cells were dedifferentiated cells or if the cells were cultured such that re-expression of extracellular matrix proteins was obtained prior to implantation. Thus, it is not known which cells were used or what the phenotypic profile of the cells were at the time of implantation. The specification further teaches that thirty-three weeks after implantation, analysis of the implants indicated that the autologous cells which were labeled with BrdU prior to implantation, were visualized by staining, the specification stating that "This staining marks autologous disc cells which were engrafted back into the donor animals" (see page 17, lines 21-23). However, the specification then states that "Arrows mark the BrdU positive cells which were engrafted or which are descendants of engrafted cells" (see page 17, lines 25-26). It is not readily apparent from these disparate statements whether the implanted cells were actually dividing, or whether the cells recapitulated the *in vivo* biosynthetic the extracellular matrix proteins profiles. Thus, from the disclosed experiments, it is not known which cells were expanded *in vitro*, and whether the implanted cells divided and expressed extracellular matrix proteins which are representative of those observed in a normal intervertebral disc *in vivo*. This information is critical given the state of the art of methods for treating intervertebral disc disorders as discussed below.

It should be noted that with regard to cell types to be implanted, it is well recognized in the art that annulus cells and nucleus cells have distinct morphologic, phenotypic and functional properties. For example, Guilak *et al.* (Spine, 24:2475-2483, 1999) teach that the intervertebral disc contains a heterogeneous population of cells, that important spatial differences exist in the morphology an phenotype of the cells between regions corresponding to the annulus fibrosus and nucleus pulposus, as well as the transition zone. The cells exhibit a biosynthetic response to mechanical loading, which may vary significantly according to region in the intervertebral disc.. Results from the studies cited by the authors indicate evidence of intrinsic variations in the response of intervertebral disc cells to mechanical stimuli both in vitro and in vivo (see, e.g., page

2475 through 2476). Similarly, Aigner *et al.* (Calcif. Tissue Int., 63:263-268, 1998) teach that the intervertebral disc consists of three distinct regions: the outer firm annulus fibrosus, the inner soft pulpy nucleus pulposus, and the hyaline cartilage-like endplate interspersed between the rest of the disc and the vertebral bodies. All of the regions consist mainly of an extracellular matrix of collagen fibrils inflated by water drawn into the disc by the high swelling pressure imparted to the disc by its proteoglycans. Aigner et al note that the organization and composition of these regions differ markedly, with the outer annulus consisting of a highly organized, dense collagen network, the inner annulus being more fibro-cartilaginous, and the nucleus consisting of a low collagen and high proteoglycan content which is highly hydrated. In view of the teachings of Aigner *et al.* and Guilak *et al.*, that intervertebral disc tissue comprises a heterogeneous population of cells, which have distinct biosynthetic capacities, and which respond to stimuli differently, and the lack of disclosure in the instant application with regard to which intervertebral disc cells to isolate, expand, and use in a method of treating intervertebral disc disease, and further in view of the lack of prior art data which teaches implantation of a particular expanded population of disc cells, it would have required undue experimentation for one of skill in the art to provide an expanded population of the appropriate intervertebral disc cell type and use the expanded population in a method for treating disc disease by implanting the cells into intervertebral disc tissue. With regard to the state of the art of implanting intervertebral disc "tissue" to a site requiring such implantation, both Frick *et al.* (Spine, 19:1826-1835, 1994), and Luk *et al.* (Clin. Orthopaed. Rel. Res., 337, 13-26, 1997) teach grafting of intervertebral disc tissue into animal models. Both Frick *et al.* and Luk *et al.* clearly indicate that while different animal models may be suitable for initial studies on intervertebral disc properties as well as for studying the effects of different therapeutic regimens for treating disc diseases, one cannot extrapolate results from these animal models to humans (see, e.g., Frick *et al.*, page 1832, under "Discussion"; and Luk *et al.*, page 23). Moreover, Luk *et al.* indicate that while there is a suggestion that after an initial period of degeneration the disc becomes stabilized and may even be able to regenerate, the extent and the effectiveness of the regenerative process is still unclear and will need further studies (see, e.g.,

page 25, left column). Thus, the state of the art is such that grafting intervertebral disc tissue for the purpose of treating disc disease is neither routine nor predictable. Given the lack of sufficient guidance in the specification and the state of the art, it would have required undue experimentation for one of skill in the art to practice the method as claimed. As the methods of treating disc disease are not enabled, the therapeutic compositions comprising *in vitro* expanded intervertebral disc cells are not enabled as well.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 are rendered vague and indefinite by the phrase "capable of" as it is unclear under what conditions the cells have the capacity to proliferate within a three-dimensional structure (claim 1) or have the capacity to re-express extracellular matrix materials (claim 3).

Claim 4 is rendered vague and indefinite by the phrase "intimate contact" as it is unclear what is meant by that phrase, i.e., the phrase does not appear to be art recognized.

Claims 7 and 9 are rendered vague and indefinite by the phrase "wherein at least a portion" as this is a relative phrase which is neither defined in the claim or in the specification. It is unclear how many cells are required to proliferate (claim 7) or re-express extracellular matrix proteins (claim 9). The metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-11, and 13-15, 17, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Gruber *et al.* (Exp. Cell Res. 235:13-21, 1997).

The claims are drawn to human intervertebral disc cells *in vitro*. Note that claims 10, 11, 13-15, 17, and 18 are included in this rejection as the intended use of the intervertebral disc cells bears no patentable weight, i.e., the intended use of the composition does not materially affect the properties of the intervertebral disc cells.

Gruber *et al.* disclose a method of isolating annulus or nucleus disc cells from human intervertebral disc tissue and culturing the tissue explant to obtain a primary cell culture. The tissue explants are plated in tissue culture flasks and anchored by placement of a nylon mesh over the explant fragments. The cells are grown at 37°C in medium containing fetal bovine serum and fed every 2 days. When primary cultures show a confluent outgrowth of cells from the nylon mesh, the cells are trypsinized and mixed with an alginate solution to form an alginate/cell suspension, and cultured in multiwell plates in the presence of a calcium chloride polymerizing solution. Alternatively, the trypsinized primary cell cultures are mixed with agarose rather than alginate. After culturing, the cells can be recovered for further use. Moreover, Gruber *et al.* disclose culturing the cells in the presence of transforming growth factor-β, and insulin-like growth factor (see pages 13-15, under Materials and Methods).

Thus, the method of culturing intervertebral disc cells described by Gruber *et al.* anticipates applicants' claims.

Claims 1-11, and 13-15, 17, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Gruber *et al.* (Matrix Biology, 16:285-288, 1997).

The claims are drawn to human intervertebral disc cells *in vitro*. Note that claims 10, 11, 13-15, 17, and 18 are included in this rejection as the intended use of the intervertebral disc cells bears no patentable weight, i.e., the intended use of the composition does not materially affect the properties of the intervertebral disc cells.

Gruber *et al.* disclose trypsinizing *in vitro* expanded annulus cells obtained from human intervertebral disc tissue and culturing the cells in alginate or agarose layers, or as monolayers. (see pages 285-286, under Materials and Methods).

Thus, the method of culturing intervertebral disc cells described by Gruber *et al.* anticipates applicants' claims.

Claims 1-11, and 13-15, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Chelberg *et al.* (J. Anat. 186:43-53, 1995).

The claims are drawn to human intervertebral disc cells *in vitro*. Note that claims 10, 11, 13-15, 17, and 18 are included in this rejection as the intended use of the intervertebral disc cells bears no patentable weight, i.e., the intended use of the composition does not materially affect the properties of the intervertebral disc cells.

Chelberg *et al.* disclose a method of growing human annulus and nucleus cells obtained from adult human intervertebral discs comprising isolating cells from the tissue, casting cells in alginate microspheres in the presence of a $CaCl_2$ solution, and incubating the cells in culture dishes in the presence of fetal bovine serum at 37°C (see, e.g., pages 44-45 under "Tissue Processing"). The cells express a differentiated phenotype, i.e., the cells synthesize glycosaminoglycans, Type I

and Type II collagens, aggrecan, and other proteoglycans (see, e.g., pages 48, right hand column, through page 50, left column). As there is no distinction between the cells of Chelberg *et al.* and the cells of the instant invention, the reference of Chelberg *et al.* anticipates the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,080,579. Although the conflicting claims are not identical, they are not patentably distinct from each other because the intervertebral disc cells and compositions comprising the cells of the instant invention are encompassed in the claimed cells of U.S. Patent No. 6,080,579. Moreover, obtaining the intervertebral disc cells in a method of expanding disc cells in vitro either as a monolayer or in a three-dimensional configuration would have been obvious in view of the by a product-by-process claims of the instant invention and the culture methods claimed in U.S. Patent No. 6,080,579. Thus, the cells, and methods of obtaining the cells of the instant invention would have been obvious in view of the claimed invention in U.S. Patent No. 6,080,579.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

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